Review

Choriocapillaris in Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is a multifactorial disease characterized by progressive alterations of different retinal structures ultimately leading to vision loss. Among these, the choriocapillaris (CC) has been found to be affected in different stages of AMD. In this review we provide a discussion on the different stages of AMD, focusing particularly on the alterations involving the CC. This has been possible thanks to the introduction of optical coherence tomography-angiography, a recently developed imaging technique which allows the detection of blood flow in choroidal vessels. Therefore, the aim of this review is to provide a description of the various alterations involving the CC in the different stages of AMD.

Keywords: Age-related macular degeneration, choriocapillaris, optical coherence tomography angiography, AMD classification

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Introduction

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is one of the principal causes of blindness worldwide and the leading cause of visual loss in western countries in people older than 55 years of age.[1] This disorder is estimated to affect 196 million people globally, among which 8.4 million suffer from a moderate to severe visual impairment.[2] The exact pathophysiologic process leading to the development of AMD is still incompletely understood. However, a combination of non-modifiable and modifiable risk factors has been implicated in the pathogenesis. The former include genetic predisposition, with the genes *CFH*, *C3*, *C2*, *ARMS2*, *FB*, *CFHR4*, *CFHR5*, and *F13B* having the strongest correlation,[1] as well as age, northern-European ancestry, and a positive family history.[2] Among the latter, only smoking is a known risk factor, although cardiovascular disease, a high body mass index, a high-fat diet, and low intake of antioxidants have also been hypothesized.[3,4]

AMD is characterized by the accumulation of uncleared cellular debris coming from the retinal pigment epithelium (RPE), called drusen, between the RPE and the inner collagenous layer of Bruch's membrane (BM). Drusen are constituted of lipids with esterified and unesterified cholesterol, as well as proteins and carbohydrates.[5]

Numerous classifications have been proposed for AMD.[4,6,7] However, the classification proposed by Ferris et al.[8] is the most widely used. This classification identifies five clinical stages: no apparent aging changes, normal aging changes, and early, intermediate, and late AMD. Grading is based on the presence of drusen and pigmentary abnormalities within the space of two disc diameters from the fovea. The first two stages are non-pathologic, early AMD is characterized by the presence of medium drusen (>63 µm and <125 µm) and the absence of pigmentary alterations, intermediate AMD (iAMD) by large drusen (>125 µm) and/or pigmentary abnormalities, and late

AMD corresponds to the presence of macular neovascularization (MNV) and/or geographic atrophy (GA).[8] Patients with early AMD are usually asymptomatic or may complain of mild central vision distortion, while later forms present with a more marked vision loss that can progress more or less rapidly in the neovascular or GA forms, respectively.[4]

In the past, the AMD diagnosis was mostly based on clinical examination. Nowadays, imaging techniques including structural optical coherence tomography (OCT) and OCT angiography (OCTA) may allow for an earlier and faster diagnosis.[4,5,6,7,8,9] In AMD the choriocapillaris (CC) can also undergo several alterations which can reflect the different stages of the disease. In iAMD, a lower number of signal voids, larger signal void average size, and greater signal void total area may be observed on OCTA.[10,11] In neovascular AMD (nAMD) and GA, the signal void size is even larger, suggesting that an impairment of the CC can lead to the development of these pathologies.[12]

The Choriocapillaris

The choroid is located between the sclera and the retina and receives blood from three branches of the ophthalmic artery.[13] The choroid is composed of three layers in the macular region: Haller's layer, Sattler's layer, and the CC.[14]

The CC, initially documented in 1702, forms the innermost layer of the choroid and consists of fenestrated capillaries situated just beneath BM. The CC represents the structure with the highest capillary density in the human body, allowing a high rate of exchange.[15]

The configuration of the CC varies across different regions of the eye. In the equatorial area, the capillaries exhibit a polygonal shape; at the periphery, they form an elongated network; in the posterior pole, they resemble a dense honeycomb structure; whereas in the peripapillary and submacular areas, they appear as a continuous aggregation of capillaries.[14,16]

Histologically, the CC typically exhibits an average height of 6.8±2.5 µm. Endothelial cells form the innermost membrane and primarily facilitate molecular exchange between BM and the blood, predominantly through fenestrations, although occasionally via intracellular transportation. Various molecules are involved in the biochemical pathways of CC cells, including transthyretin, heparin, and fibronectin. It is also important to highlight the role of vascular endothelial growth factor (VEGF) in the physiological choroidal development, as it is also involved in the neovascular form of late AMD.[14] The CC has numerous other functions in addition to paracellular fluid exchange through fenestrations. The hydrostatic and oncotic pressures inside its vessels help maintain retinal attachment and can influence intraocular pressure. Additionally, CC flow can vary throughout the day, typically peaking in the morning and responding to postural changes.[14]

Several previous studies have investigated the CC histologically, especially in eyes with GA. McLeod et al.[17] analyzed postmortem choroids from 11 subjects, including controls, GA patients, and individuals with nAMD. They utilized methacrylate embedding and sectioning to assess structural changes, revealing that while GA regions exhibited evident loss of RPE, the CC could remain intact. This led the authors to propose that the primary insult in GA likely begins at the RPE level, followed by subsequent CC degeneration. Seddon et al.[18] investigated postmortem choroids from 36 subjects, including controls and AMD patients with varying disease stages, including GA. They employed *Ulex europaeus* agglutinin (UEA) lectin staining and confirmed a significant reduction in the CC in eyes with GA, particularly in regions of RPE atrophy. Despite some persistence of CC vessels within GA regions, their diameter was notably reduced, indicating both morphological and functional changes in these surviving vessels. Lastly, Edwards et al.[19] conducted a recent analysis on postmortem choroids from eight subjects, including controls and individuals with GA, with available imaging data prior to death for clinicopathologic correlations. Using UEA lectin staining, they observed severe CC dropout directly corresponding to areas of RPE atrophy in GA eyes. Surviving CC vessels in these regions appeared constricted. Conversely, CC vessels in regions with intact RPE resembled those in healthy controls.

OCTA to Assess the CC

OCTA offers several advantages over fluorescein angiography (FA) and indocyanine green angiography (ICGA), including its non-invasive nature which eliminates the need for contrast agent injections and reduces the risk of allergic reactions.[20,21] Additionally, OCTA provides higher resolution visualization of deeper layers. However, it lacks the ability to dynamically interpret blood transit and visualize leakages. Interpretation of OCTA images may be challenging in the presence of pathological alterations such as retinal neovascularization or drusen, as these can interfere with the passage of the laser beam.[22,23] Furthermore, small vessels may not be clearly identifiable on OCTA due to slow blood flow, and any eye movement can result in artifacts, complicating image interpretation.[24]

OCTA is an imaging technique used to visualize blood flow in retinal and choroidal vessels. It works by acquiring multiple B-scans of the same area to generate three-dimensional volumetric data, providing a representation of the vascular lumen.[22] OCTA images of the CC typically have a granular appearance, which helps distinguish this vascular layer from the underlying layers.[25,26,27,28] To improve image quality and enhance visualization of CC vessels,[28,29,30] image averaging can be employed, transforming the granular pattern into a meshwork and rendering vessel segments more continuous.[14,31]

OCTA images of the CC typically display "flow voids", which manifest as small dark regions that possibly represent intercapillary spaces, alongside brighter areas indicative of blood flow within the CC.[11,21] Interestingly, there's been a suggestion to rename "flow voids" as "signal voids", as it's challenging to distinguish blood flow below the decorrelation threshold.[32] Also interestingly, there exists a mathematical power law relationship between the number and size of these voids, with a constant correlated to factors such as age, hypertension, and the presence of late AMD in the fellow eye.[10] Studies have indicated that the

increase in flow deficits with aging is more pronounced in the fovea.[33] This is probably due to the higher production of waste metabolites in the foveal region, which puts the CC under greater stress.[14]

Overall, there are some limitations in studying the alterations of the CC in different stages of AMD. These include several artifacts that may limit the assessment of the CC.[21]

CC in Intermediate AMD

In AMD, the CC can undergo various alterations, which differ according to the stage of the disease.[34] In iAMD, drusen are predominantly found in areas of the choroid with a reduced perfusion of the CC. This has been extensively confirmed by OCTA studies showing that flow deficits are heightened in regions where drusen and reticular pseudodrusen are located (Figure 1).[14,35] This observation has led to the hypothesis that the degeneration of endothelial cells can contribute to drusen formation.[14]

In one of the first investigations on this subject, 42 patients (42 eyes) diagnosed with iAMD were compared with 20 healthy controls (20 eyes).[32] The analysis involved quantifying the area of the CC with non-detectable perfusion, indicating total dropout of CC vessels, and determining the average signal void size in the CC with an OCTA device. To ensure accurate analysis, areas directly beneath drusen and major retinal vessels were excluded to minimize the influence of shadowing and projection artifacts. Additionally, patients with iAMD were categorized based on fellow eye status, resulting in two groups: patients affected by bilateral iAMD and those affected by unilateral iAMD with nAMD in the other eye. The study revealed no disparities in the area of non-detectable CC perfusion among the three groups. However, patients with unilateral iAMD exhibited a significant increase in average CC signal void size compared to both bilateral iAMD cases and healthy individuals. Given that eyes affected by iAMD are more likely to progress to nAMD if the fellow eye has nAMD,[36] these findings support the presence of an ischemic choroidopathy that may predispose to neovascularization development. Consequently, alterations in the CC seem to play a crucial role in nAMD pathogenesis. A notable limitation of that study was the inability to assess the CC beneath drusen due to the use of a spectral domain device for image analysis. Nonetheless, previous histopathological research has indicated that drusen tend to form in areas of altered vascularization,[6] suggesting that OCTA might reveal areas with different CC perfusion among patients with iAMD.

To investigate potential topographical discrepancies in CC perfusion among patients with iAMD, a follow-up study utilized a swept source OCTA device.[37] This device offered enhanced assessment capabilities under drusen due to its longer wavelength, which improves penetration through the RPE.[11,38,39] In this study, 30 eyes with iAMD and 30 healthy controls were prospectively included. Notably, CC images were examined in three distinct regions to enable a topographical analysis: (i) within the region with drusen, (ii) within a 150 µm-wide ring surrounding the margin of drusen, and (iii) in drusen-free regions. Comparative analysis with controls revealed that iAMD eyes exhibited a lower number of signal voids, larger average signal void size, and larger total signal void area. Particularly significant differences in these parameters were observed in regions underneath and adjacent to drusen, supporting earlier findings suggesting that drusen tend to form over areas of altered vascularization.[6]

Imaging of the retina has been utilized to study dysfunction of the outer retina resulting from CC impairment in iAMD eyes. A histopathological study by Curcio et al.[40] revealed an important decrease in the number of photoreceptors in eyes with drusen.

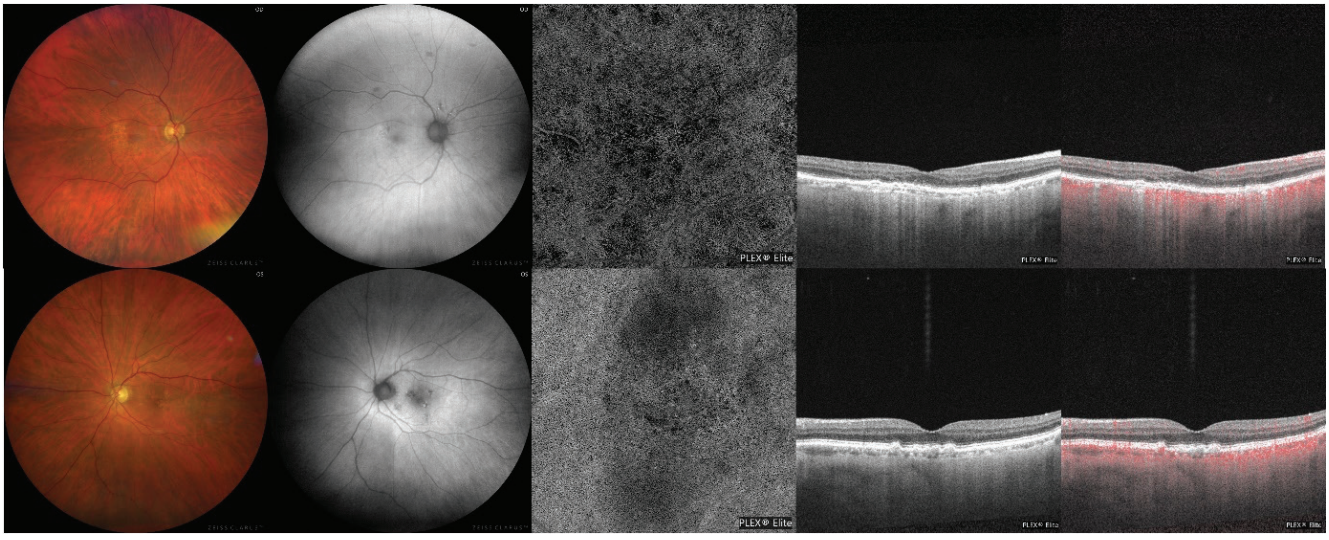

Figure 1. Multimodal imaging from a patient with intermediate age-related macular degeneration: fundus photography (left), green autofluorescence (left-middle), *en face* optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). Drusen larger than 125 µm can be observed on structural OCT, and the *en face* OCTA image segmented at the level of the CC demonstrates areas of hypoperfusion in this vascular layer

Additionally, Boretsky et al.[41], using adaptive optics scanning laser ophthalmoscopy, demonstrated a progressive decline in the density of photoreceptors across different AMD stages. Given the importance of CC flow for sustaining photoreceptors, the reduced CC perfusion in AMD eyes may potentially contribute to photoreceptor damage through an ischemic mechanism. Consequently, multimodal imaging techniques were used to investigate the correlation between CC alterations and photoreceptor disfunction in iAMD eyes.[42] Photoreceptor damage was quantitatively evaluated through analysis of the reflectivity of *en face* OCT images obtained at the ellipsoid zone (EZ). The signal from the EZ originates from ellipsoids in the most internal segment of photoreceptors, which are densely filled with mitochondria.[43] Since both photoreceptor damage and dysfunction can manifest as areas with decreased reflectivity on *en face* images, several studies have evaluated EZ reflectivity as a surrogate for photoreceptor dysfunction.[44,45] However, several patient characteristics (e.g., cataracts) can greatly influence structural brightness, which poses a significant challenge in using *en face* structural OCT to assess the reflectivity of photoreceptors and complicates cohort comparisons. To address this issue, several studies have "normalized" the images.[44,45]

A study involving 35 patients with iAMD and 35 healthy controls utilized swept source OCT and OCTA imaging to establish a topographical correlation with photoreceptor and CC impairment, respectively.[42] This investigation revealed that in eyes with iAMD, the "normalized" EZ reflectivity was notably reduced even in areas devoid of drusen. These findings indicate an important and widespread alteration of photoreceptors. Notably, a positive association was observed between the "normalized" EZ reflectivity and CC perfusion in drusen-free regions. However, no such relationship was identified in regions with drusen or in healthy eyes. Consequently, these results suggest a pathological connection between photoreceptor impairment and CC perfusion in AMD, particularly in regions devoid of drusen.

Another study assessed the association between photoreceptor dysfunction and CC vascularization using multifocal electroretinogram (mfERG) and OCTA, respectively, in 17 eyes of 17 patients with iAMD.[46] Overall, the findings revealed a direct relationship between N1 implicit time and both total signal void area and average signal void size. The N1 wave is believed to stem from post-receptor signals after cones, whereas the P1 wave is derived from the inner retina. Therefore, it was hypothesized that changes in the CC mostly impact post-photoreceptor function. Moreover, the correlation between CC changes and mfERG implicit time, rather than the amplitude of the response, suggests a connection with neuroretinal functional alterations instead of actual cell loss.[47]

CC in Neovascular AMD

nAMD represents a form of late AMD characterized by angiogenesis stimulated by various proinflammatory and proangiogenic cytokines, including VEGF. These cytokines can be secreted by immune cells infiltrating the macula or, more importantly, by RPE cells.[48] Pathologic vessels can originate from either the choroidal or retinal circulation.[8] Hence, the term MNV is preferred over choroidal neovascularization. Three types of MNV have been identified: type 1, type 2, and type 3.[49]

Both types 1 and 2 involve vessel growth from the CC: type 1 manifests beneath the RPE layer, while type 2 penetrates BM and the RPE, proliferating into the subretinal space. In contrast, type 3 MNV originates from the retinal circulation.[49] Histologically, macrophage infiltration near MNV areas, deposits in BM, and ghost CC are commonly observed.[14] Newly formed vessels usually present without fenestrations[14] and the leakage of proteinaceous material occurs mostly through transendothelial channels.[17]

The CC has been extensively studied using OCTA in patients with nAMD (Figure 2).[34] In type 1 MNV, the presence an area

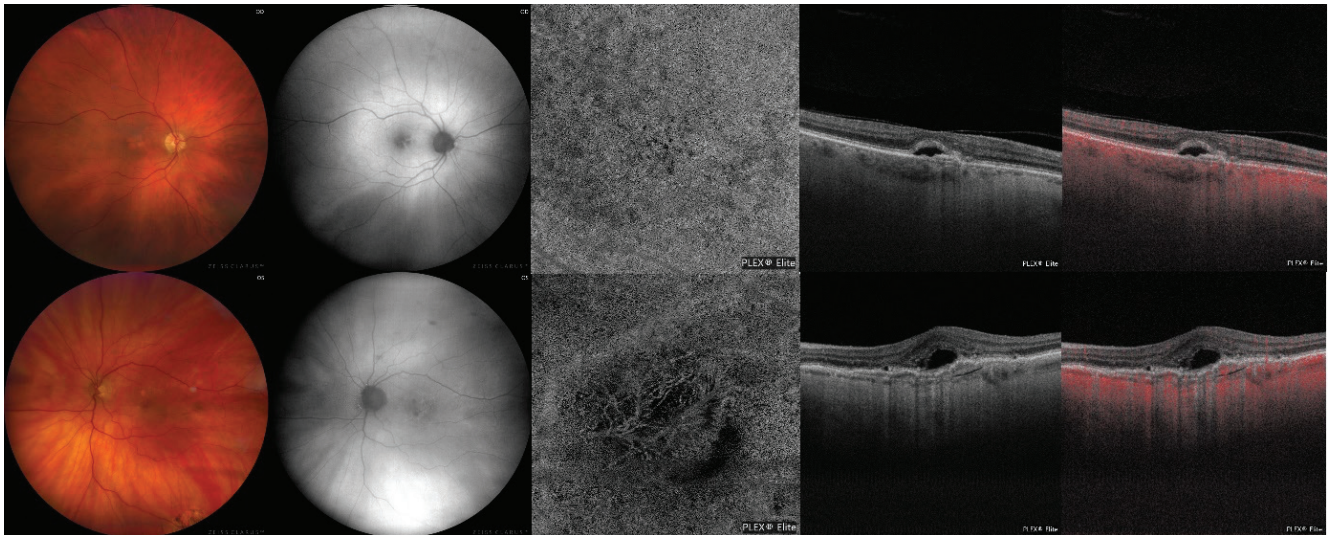

Figure 2. Multimodal imaging from a patient with neovascular age-related macular degeneration: fundus photography (left), green autofluorescence (left-middle), optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). On the *en face* OCTA image, macular neovascularization is evident around a region of CC hypoperfusion

of CC non-perfusion around the lesion has been demonstrated, which was termed "dark halo". It is still not clear if this darkening effect is due to the presence of blood or subretinal or intraretinal fluid, and it is also not fully understood whether the dark halo area indicates ischemia of the CC or is a shadowing effect.[35,50]

The emergence of type 3 MNV is believed to be linked to an alteration in the balance between VEGF and other cytokines coming from the RPE.[51] Studies have demonstrated that untreated nAMD eyes with type 3 MNV exhibit significantly higher levels of VEGF in the aqueous humor compared to eyes with MNV of type 1 or 2, which arise from the choroid instead of the retina. [51] Consequently, it has been proposed that outer retinal ischemia plays a crucial role in driving the development of this MNV subtype. This theory finds support in structural OCT studies, which have revealed a thinning in the choroid in individuals with AMD and type 3 MNV.[52,53]

Given the pivotal function of the CC in nourishing the outer retina and RPE, several OCTA studies have delved into the characteristics of the CC in eyes affected by type 3 MNV. In an OCTA investigation, the CC was quantitatively assessed in eyes with type 3 MNV and the unaffected (i.e., having no signs of MNV) fellow eyes of 21 patients.[54] Furthermore, these unaffected eyes were compared with the unaffected fellow eyes of 20 patients with unilateral type 1 or 2 MNV. The OCTA analysis revealed that eyes with type 3 MNV had significantly higher total signal void area and average CC signal void size (representing CC hypoperfusion) when compared with unaffected fellow eyes. These findings suggest that CC hypoperfusion may lead to ischemic abnormalities of the RPE, ultimately contributing to the development of type 3 MNV. Importantly, the unaffected fellow eyes of patients with unilateral type 3 MNV exhibited more pronounced CC impairment compared to the unaffected fellow eyes of patients with unilateral type 1/2 MNV. These results hint at a potential bilateral effect of CC hypoperfusion in patients with unilateral type 3 MNV, which could partly elucidate the heightened risk of these unaffected eyes eventually developing type 3 MNV.

Another study utilizing swept source technology and image compensation with structural information reaffirmed previous observations of decreased CC perfusion in eyes with type 3 MNV.[55] This investigation included 26 eyes with type 3 MNV (21 patients) and 26 eyes with iAMD (17 patients). Compared to eyes with iAMD, both the total signal void area and the average CC signal void size were elevated in eyes with type 3 MNV. Collectively, findings from OCTA studies support the notion that CC alterations may indeed play a significant role in the development of type 3 MNV, potentially even more so than in eyes with type 1/2 MNV.

Choriocapillaris in Geographic Atrophy

GA is a form of late, non-exudative AMD characterized by atrophy of the RPE and outer retina, along with significant impairment of the CC (Figure 3).[56]

OCTA images have revealed impaired CC perfusion primarily within areas of RPE atrophy in GA.[56,57,58,59] However, some hypoperfusion has been observed in regions with intact RPE, particularly along the GA border. Importantly, perfusion levels at the GA border serve as a significant biomarker for GA progression. Specifically, reduced perfusion in the GA border has been linked to faster GA progression over time. Finally, the CC was demonstrated to be impaired in regions of nascent GA, further suggesting that CC changes may precede a definite atrophy of the RPE.[60]

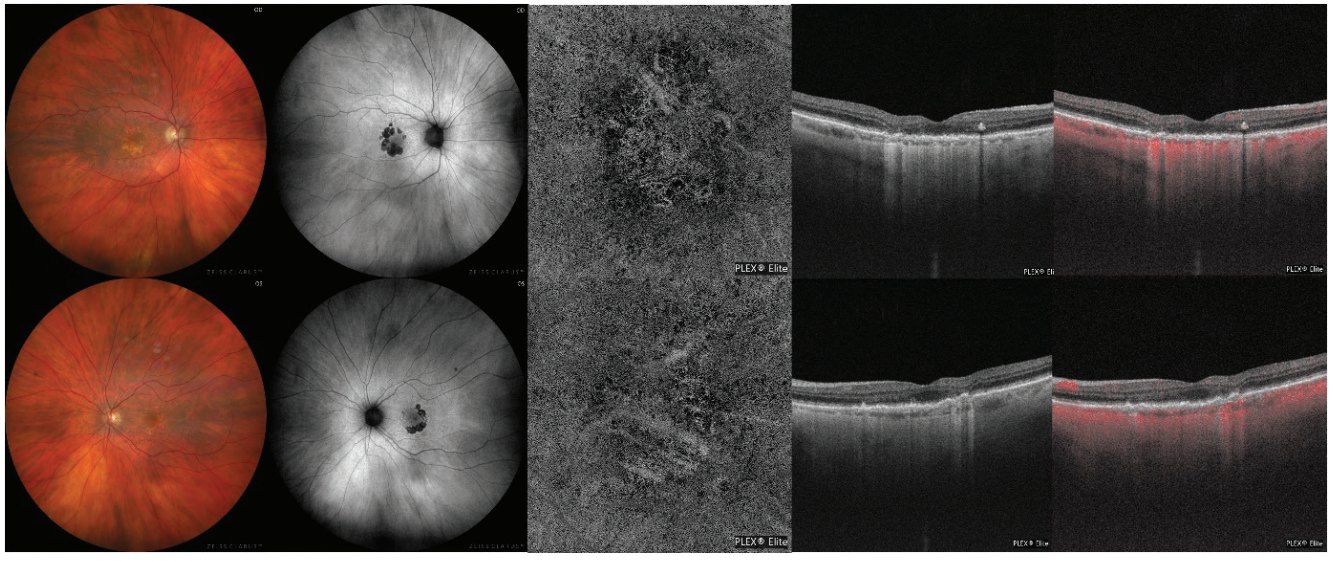

Figure 3. Multimodal imaging from a patient with geographic atrophy: fundus photography (left), green autofluorescence (left-middle), *en face* optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). In the *en face* OCTA image segmented at the level of the CC, there is a noticeable diffuse hypoperfusion of the CC, primarily co-localizing with the region exhibiting geographic atrophy. Interestingly, the absence of the CC causes a better visualization of the outer choroidal vessels, which are usually not visible in physiological conditions

Conclusion

AMD is a leading cause of visual impairment worldwide, impacting various structures within the eye. The CC is significantly affected in AMD, with pathologic changes varying across disease stages. The advent of OCTA has notably enhanced our understanding of these alterations, offering advantages over conventional FA and ICGA. This review aimed to underscore the newfound insights into the role of the CC in AMD, which are vital for elucidating its pathogenesis and facilitating the delivery of optimal therapy for affected patients.

Ethics

Authorship Contributions

Concept: All authors, Design: All authors, Literature Search: G.N., Writing: G.N., E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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